AD-A194 752 TREATMENT WITH TYROSINE A NEUROTRANSMITTER PRECURSOR REDUCES ENVIRONMENTA. (U) ARMY RESEARCH INST OF ENVIRONMENTAL MEDICINE NATICK MA L E BANDERET ET AL. 1/1

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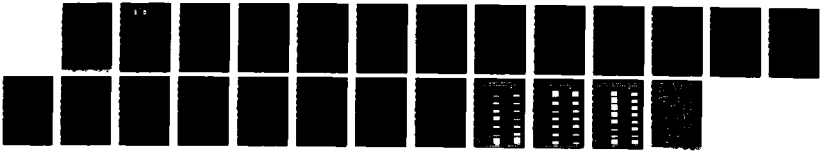

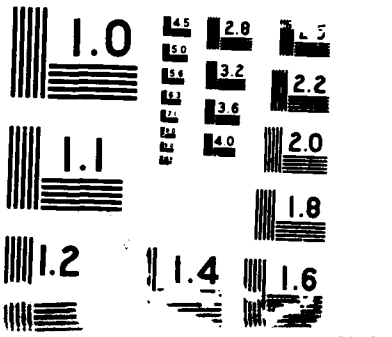
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Acutely stressful situations can disrupt behavior and deplete brain norepinephrine and dopamine, central catecholaminergic neurotransmitters. In animals, administration of tyrosine, a large neutral amino acid and dietary precursor of the catecholamines, reduces these behavioral and neurochemical deficits. We investigated whether tyrosine (100 mg/kg) would protect humans from some of the adverse consequences of a 4.5 hour exposure to a combination of environmental stressors. Tyrosine decreased symptoms, adverse moods, and performance impairments in subjects with average or greater responses to cold and high altitude exposure. This suggests that treatment with tyrosine may benefit humans experiencing acutely stressful situations, perhaps by affecting central catecholamines.

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TREATMENT WITH TYROSINE, A NEUROTRANSMITTER PRECURSOR, REDUCES ENVIRONMENTAL STRESS IN HUMANS

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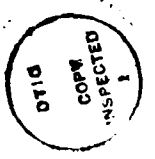
ABSTRACT

Acutely stressful situations can disrupt behavior and deplete brain norepinephrine and dopamine, central catecholaminergic neurotransmitters (1). In animals, administration of tyrosine, a large neutral amino acid and dietary precursor of the catecholamines, reduces these behavioral and neurochemical deficits (2). We investigated whether tyrosine (100 mg/kg) would protect humans from some of the adverse consequences of a 4.5 hour exposure to environmental stressors. Tyrosine significantly decreased symptoms, adverse moods, and performance impairments in subjects who exhibited average or greater responses during cold and high altitude exposure. This suggests that treatment with tyrosine may benefit humans experiencing acutely stressful situations, perhaps by affecting central catecholamines.



Animals that have been acutely stressed exhibit characteristic neurochemical and behavioral changes (1). In certain brain regions utilization of norepinephrine and other neurotransmitters increases substantially and norepinephrine levels decline; concurrently, the animals explore less, display less interaction with their environment, and seem debilitated (1). Tyrosine, given acutely or in the diet, protects rodents from both the neurochemical and the behavioral effects of such acute stressors as tail shock or a cold swim (3).

Tyrosine is an amino acid found in dietary proteins and is the precursor of norepinephrine, dopamine, and epinephrine (2). During stressful situations, active catecholaminergic neurons may require additional quantities of this precursor so that brain catecholamine synthesis will keep pace with the increased amounts of neurotransmitter being released (2). Some of the behavioral deficits caused by acute stress may result from depletion of norepinephrine, and perhaps dopamine, in particular catecholaminergic neurons (4). Noradrenergic neurons within the locus coeruleus are thought to influence attention, alertness, motor activity, and anxiety (4). Thus, tyrosine could protect against adverse behavioral effects of acute stress by preventing depletion of norepinephrine in such neurons. To our knowledge tyrosine's effects on experimentally stressed humans have not been examined previously; among unstressed subjects its administration resulted in small improvements in mood and reaction times (5).

We evaluated tyrosine using a combination of environmental stressors---cold and simulated high altitude; these treatments produce measurable changes in symptoms (6), mood (7), and performance (8). Acute cold exposure depletes central catecholamines and impairs various behaviors in rodents (1). Also, high altitude (hypoxia) causes changes in performance and mood soon after ascent to altitde (e.g. 8).

Twenty three male U.S. Army personnel, aged 18-29 years (median = 21), participated in this experiment. All were volunteers and gave their informed consent after they were fully appraised of the potential risks and benefits of the study (9).

The volunteers were all exposed to two levels of environmental stressors: 1) 15 °C and 4200 m simulated altitude and 2) 15 °C and 4700 m simulated altitude. High altitude conditions were simulated by reducing atmospheric pressure (10). Exposure to a cold and hypobaric environment resembles conditions encountered by humans who travel to mountainous regions. The altitudes we selected were slightly less and slightly greater than Pikes Peak, Colorado. A control condition with normal temperature and pressure conditions (22 °C and 550 m altitude) was also included.

Tyrosine was compared to placebo with a crossover design. Subjects were tested with both placebo and tyrosine for each of the three environmental conditions. Each environmental exposure (control condition, lessor stressor, or greater stressor) was 4.5 h per day. The actual environmental condition was unknown to the subjects until they experienced it.

Tyrosine or placebo was administered double-blind, in gelatin capsules, and in two equal doses (11). On a given test day about half of the subjects received tyrosine; the others received placebo (12). Test sessions began at 7:00 A.M. The first dose (50 mg/kg) was given after 20 min, just before we exposed subjects to the environmental condition. The second dose (50 mg/kg), 30 min after the first. The total dose was about 80% of an adult's daily dietary intake. Blood samples (<20 ml) were drawn from an arm vein just before the first dose of tyrosine or placebo, and 150 and 265 min later and used for determination of plasma tyrosine concentrations (13). At least 48 h separated test sessions. We studied separate groups of 7, 4, and 12 subjects for 20 days each.

Cold and high altitude environments produce many adverse effects; we measured symptoms, mood states, cognitive performance, reaction time, and vigilance (14). Subjects rated their symptoms with the Environmental Symptoms Questionnaire (6). Mood states were evaluated with four scales that have been employed to evaluate a variety of psychoactive drugs, foods, environmental conditions, and behavioral disorders (7,15): 1) The Clyde Mood Scale, 2) Multiple Affect Adjective Check List, 3) Profile of Mood States, and 4) Stanford Sleepiness Scale. We also designed a questionnaire, the Catecholaminergic Effects Scale, to evaluate behavioral changes that might result from the neurochemical consequences of administering tyrosine. The tasks for assessing cognitive performance required focusing of attention, applying prior knowledge to problems, processing spatial and verbal information, performing mathematical calculations, and making decisions (16). We also measured reaction time (17) and vigilance (18).

To insure that the treatment strategy was evaluated in subjects that were impaired by exposure to the environmental stressors, we selected individuals who were most affected by exposure to cold and high altitude. We defined responders, for each dependent measure and level of environmental stressor, based upon their scores when they were treated with placebo (19).

The combination of cold and simulated high altitude exposure produced many statistically significant symptoms, adverse moods, and impairments in performance, in subjects treated with placebo. As expected (21), we observed marked variability between subjects; some subjects experienced minimal effects. Also, some dependent variables were not affected by the environmental stressors.

Typically, symptom intensities in selected subjects were five times greater during stressful environmental conditions than during the control environmental condition, while headache and coldness were seven and fourteen

times greater, respectively. Mood states (negative scale type) were two times greater; moods (positive scale type) decreased 10%. Performances (positive scale type) decreased 5 to 20%; whereas, choice reaction time errors increased 100%. Vigilance performance was 65% of the control value.

Plasma tyrosine levels were significantly increased following tyrosine administration. Baseline levels of plasma tyrosine before treatment with tyrosine was 42.7 $\pm$ 3.3 nmoles/ml, averaged across all environmental conditions. Plasma tyrosine levels were 108.5 $\pm$ 5.1 nmoles/ml, 150 min after ingestion of tyrosine. After 265 min, plasma levels decreased slightly to 98.6 $\pm$ 6.3 nmoles/ml. Neither level of environmental stressor changed plasma tyrosine concentration during tyrosine or placebo treatment. Heart rate and blood pressure did not differ as a function of tyrosine treatment condition for any level of environmental conditions.

Tyrosine significantly reduced many adverse behavioral effects caused by exposure to cold and high altitude stressors. Figure 1 shows treatment data from the Environmental Symptoms Questionnaire, Stanford Sleepiness Scale, and the Catecholaminergic Effects Scale. Tyrosine, compared to placebo, significantly reduced symptoms of headache, coldness, distress, fatigue, muscular discomfort, and sleepiness during exposure to at least one level of the environmental stressors. Tyrosine was also beneficial as measured by the Catecholaminergic Effects Scale. Overall, tyrosine treatment reduced all symptoms with significant treatment effects by 20-40% (median = 30%). Similarly, tyrosine overcame 85-95% of the impairments measured by the Catecholaminergic Effects Scale.

Tyrosine also reduced adverse emotions experienced during exposure to the environmental stressors. Fig. 2 shows some mood states from the Clyde Mood Scale, Multiple Adjective Affect Check List, and the Profile of Mood States. During exposure to the environmental stressors, tyrosine treatment reduced

symptomatology of dizziness, confusion, fatigue, unhappiness, hostility, and tension. The subjects also reported they could think more clearly. All measures of mood, with significant treatment effects, improved by 10-88% (median = 31%). Clear thinking improved most, i.e. 88%.

Subjects' functional capacities were also impaired by exposure to the cold and high altitude conditions. Treatment with tyrosine reversed many of these adverse effects (Fig. 3). Subjects, exposed to the lessor environmental stressor, completed more Addition, Coding, Map Compass Applications, Number Comparison, and Pattern Recognition problems correctly. They also had decreased Choice Reaction Time latencies and fewer errors. Dual Task performance did not differ as a function of treatment condition.

Beneficial effects from tyrosine were also apparent during the greater environmental stressor. Tyrosine increased the number of correctly completed Number Comparison and Pattern Recognition problems, increased vigilance (Dual Task), and significantly decreased latencies on the Choice Reaction Time task. The remaining tasks in Fig. 3 were not affected by the treatment. Overall, tyrosine improved performances with significant treatment effects by 10-84% (median = 62%).

In this study tyrosine reduced adverse behavioral effects caused by exposure to cold and high altitude without apparently producing any side effects. Specifically, tyrosine decreased symptom intensities, adverse moods, and performance impairments. We evaluated 37 different behavioral measures and 22 yielded significant treatment effects for at least one level of the environmental stressor. Some of the other variables such as "aggressiveness" and "exertion" were not affected by exposure to cold and simulated high altitude. We observed positive effects of tyrosine at both levels of the environmental stressors thereby providing an internal replication of the treatment effect in this study.

In our analyses, we selected those subjects most affected by an environmental stressor to evaluate the treatment strategy. We assumed that unless a behavior (e.g. mood, performance) was impaired, it could not improve with treatment. This strategy is consistent with the neurochemical rationale for treating individuals with tyrosine to overcome neurotransmitter deficits; individuals must have deficiencies before they will benefit from tyrosine supplementation (2). Catecholaminergic neurons only appear to be responsive to additional substrate when they are highly active (22). Presumably, individuals with the largest stress-induced impairments have the greatest central deficits in catecholaminergic functioning. In generalizing to other situations, our study suggests that beneficial effects of tyrosine will be observed in subjects most affected by environmental or other stressors (23).

Many of the behavioral functions we found to be affected by treatment with tyrosine are believed to be regulated, in part, by noradrenergic neurons in the locus coeruleus. For example, anxiety (tension), vigilance, and attention are behaviors modulated by these neurons (1,4). Therefore, the beneficial effects of tyrosine that we observed are consistent with expected neurochemical changes in central catecholaminergic function.

This study demonstrates that tyrosine reduces the effects of cold and high altitude on human behavior. Tyrosine reduced the adverse effects of these acute environmental stressors on various symptoms, moods, cognitive performance, reaction time, and vigilance. Further research will be needed to determine whether tyrosine's beneficial effects generalize to other situations.

TABLE CAPTION

Table I. Psychometric instruments used to assess symptoms, catecholaminergic effects, mood states, cognitive performance, reaction times, and vigilance in this study. Indented items in the left column are symptom or mood factors. The next column lists the scale type for each measure. Negative scales indicate beneficial effects when their values decrease; positive scales, when they increase. The center column shows the medium used to administer the assessment instrument: C = portable computer, P = paper and pencil, S = computer cards. The next column shows the number of items completed for untimed measures or the test duration for timed tasks. The rightmost column shows when we administered each measure during a test session.

FIGURE CAPTIONS

Fig. 1. Effects of tyrosine treatment (mean $\pm$ sem) as measured by the Environmental Symptoms Questionnaire, Stanford Sleepiness Scale, and the Catecholaminergic Effects Scale. In all figures, histograms for an environmental condition show data for those subjects that were most affected. The solid bars are for tyrosine treatment; the cross-hatched bars are for placebo treatment. All measures shown had a significant treatment effect for one or both of the environmental conditions. An asterisk(s) indicates the level of statistical significance ($p \leq 0.05$ = *, $p \leq 0.01$ = **, and $p \leq 0.001$ = ***).

The Environmental Symptoms Questionnaire (6) consisted of 67 statements describing various somatic complaints. The Stanford Sleepiness Scale (15) had seven statements describing a sleepiness-alertness continuum. Subjects marked the statement that described how they felt. The Catecholaminergic Effects Scale consisted of adjectives or short statements such as "able to react well" that subjects rated.

Fig. 2. Tyrosine treatment effects (mean $\pm$ sem) as measured by factors from the Clyde Mood Scale, Multiple Affect Adjective Check List, and the Profile of Mood States (15). Subjects rated adjectives such as "troubled" from the Clyde Mood Scale on a 4-point continuum using a card sorting technique. Subjects arranged computer cards into categories to show their ratings for the adjectives. Subjects checked adjectives on the Multiple Affect Adjective Check List such as "panicky" if it applied to them. The Profile of Mood States consisted of adjectives such as "lively". Subjects rated each adjective with a 5-point continuum with verbal descriptors. Table I shows the statistically derived factors for these mood scales.

Fig. 3. Tyrosine treatment effects (mean ± sem) as measured by cognitive, reaction time, and vigilance tests. Addition required summing many problems; each had three 2-digit numbers. Coding involved substituting nine symbols for a numerical series from a code table, a task like encoding messages. Map Compass Applications did not use compasses or terrain maps but required conceptual understanding of their principles (24). When subjects performed the Number Comparison task, they decided if two numbers were the same or different. Each Pattern Recognition problem consisted of a model histogram and eight samples. Subjects identified the sample pattern that was the same as the model. Finally, Tower Task is our paper and pencil version of the Tower of Hanoi puzzle. Performance on each cognitive task was defined as number of problems correct per min.

In the Simple Visual Reaction Time test the subject was instructed to respond as quickly as possible to a nonperiodic visual cue on his computer screen. Four-Choice Visual Reaction Time measured visual vigilance and resembled the Wilkinson Four-Choice Reaction Time Task (17). During each trial, a stimulus appeared at one of four locations on the display. The subject pressed one of four keys on the keyboard to show the location of the stimulus. Subjects performed two tasks simultaneously on the Dual Task Vigilance Test. One task was a modification of the Bakan Vigilance Test; the other, required "estimation of two classes of events in a signal stream" (18).

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9. Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

10. All testing was in a hypobaric chamber acility at the U.S. Army Research Institute of Environmental Medicine at Natick, MA. The atmospheric pressure was 710, 450, or 421 Torr for a simulated altitude of 1800, 4200, or 4700 m, respectively. The relative humidity was 30-50%; ventilation was 0.71 m^3/min. Subjects wore the summer camouflage fatigue uniform and sat on metal chairs during testing.

11. Each test morning at 6:40 A.M., subjects ate a light breakfast (apple or cranberry juice and two cereal bars). Water and decaffeinated coffee were also available. Subjects refrained from alcohol consumption at least twenty four hours before each test day. The evening before a test session they stayed in a special sleeping area and fasted from 9 P.M. Sleeping was encouraged after the ambient lighting was turned off at 11:30 P.M.

12. During each of the two test weeks, we investigated the two levels of environmental stressors and the control environmental condition. The order of the environmental conditions was counterbalanced across groups but was the same each week for a group of subjects. Each test day of the first week the administration of tyrosine or placebo was random for each subject. Each test day of the second week, it was the inverse.

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14. We also measured blood pressure and heart rate with computerized instruments before, 60 min, and 210 min into the test session.

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Printed directions on the subjective symptom and mood scales instructed subjects to rate how they perceived themselves at that moment.

16. Methods for cognitive testing resembled those for the Performance Evaluation Tests for Environmental Research Program. Initially, we created 15 alternate (equivalent) forms of our task materials on the computer and displayed them with a laser printer. The subjects trained and practiced the performance tests 15 times in the 5 days before the start of the test sessions. Subjects trained in normal pressure and temperature conditions (75 m + 22 ^{o}C).

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17. R. Wilkinson, and D. Houghton, Beh. Res. Meth. Inst. 7, 441-446 (1975). The computer logged errors of commission (subject responded before the stimulus) and errors of omission (response latency > 1 sec) on the Visual Reaction Time and the Four-Choice Visual Reaction Time Tasks. We analyzed the number of errors of commission on the later task and individual (average) reaction times on both tasks.

18. A. P. Smith and C. Miles, Neuropsychobiol. 16, 117-120 (1986).

The vigilance component presented a three-digit number on the computer screen every 2.25 sec. Each number usually differed from the previous number by one digit, however, occasionally, the number was the same. Each subject had to detect such repetitions and press a key.

For the signal estimation test, the computer simultaneously displayed a single letter or number to the right of the three-digit number. Every 200 trials, the stimuli stopped and the subject estimated the proportion of letters. We analyzed the number of critical stimuli correctly detected by each subject on the Dual Task Vigilance Test. On the second task the proportion of letters could vary from 0.2 to 0.8 in a 200 trial series.

19. When a subject was exposed to an environmental stressor, his score (for each symptom, mood, and performance measure) was compared to his score for the control environmental condition. The subject was classified as a responder if this difference score was equal to or greater than the group mean. Responders' scores, after treatment with tyrosine and with placebo, were compared for treatment effects with t-tests. T-tests (repeated measures) were used for each level of environmental stressor rather than an ANOVA on all scores since this permitted the maximal use of data from each subject. Some subjects could not be tested under all stressful conditions (20) and our selection procedures for responders often yielded a different number of subjects (6-14; 9 = median) in the two environmental stressor conditions.

20. Six subjects did not participate in at least one test session. These individuals had blocked sinuses, head colds, or ear infections prior to testing so they could not be exposed safely to changing atmospheric pressures.

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23. We also analyzed the data from those subjects who were least affected by the environmental stressor. Tyrosine never decreased symptoms, decreased adverse mood changes, or increased performance in these subjects. *This is not surprising since these subjects experienced* few adverse effects from the environmental stressor.

24. Some problems required calculation of grid coordinates; others, understanding the relative positions of individuals from grid coordinates or the direction of travel after a change in azimuth.

25. A preliminary report of data from this project was presented at a NATO conference, "Biochemical Enhancement of Performance", and published in its proceedings. L.E. Banderet et al., AGARD Conference Proceedings, No. 415, pp. 3-1 to 3-12 (1987).

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

26. Many peoples' contributions are critical for the success of an experiment. We acknowledge Ms. B.L. Shukitt, Ms. G. Garfield, Dr. R.P. Francesconi, Dr. R.F. Goldman, MAJ T.M. Rauch, COL D.D. Schnakenberg, LTC G.F. Meadors III, Mr. Raymond V. Spring, Dr. B. Chew, and many other individuals. We thank members of the Altitude Research Division for their support of the study and operation of the Altitude Chamber facility. Lastly, we commend the twenty three soldiers who gave blood samples, endured harsh environments, and persisted during demanding behavioral assessments. Their professionalism was evident in their spirit and dedication to duty.

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TABLE I

MEASURE	SCALE TYPE	MEDIUM	NO. ITEMS (TIME IN MIN)	CUMULATIVE EXPOSURE BEFORE TESTING (MIN)
SYMPTOMS AND GLOBAL OUTCOME				
ENVIRONMENTAL SYMPTOMS QUESTIONNAIRE		C	67	260
CEREBRAL (HEADACHE)	NEGATIVE			
RESPIRATORY	NEGATIVE			
EAR/NOSE/THROAT	NEGATIVE			
COLDNESS	NEGATIVE			
DISTRESS	NEGATIVE			
ALERTNESS	POSITIVE			
EXERTION	NEGATIVE			
MUSCLE DISCOMFORT	NEGATIVE			
FATIGUE	NEGATIVE			
STANFORD SLEEPINESS SCALE	NEGATIVE	P	1	238
CATECHOLAMINERGIC EFFECTS SCALE	POSITIVE	C	44	270
MOOD STATES				
CLYDE MOOD SCALE		S	48	220
FRIENDLINESS	POSITIVE			
AGGRESSIVENESS	NEGATIVE			
CLEAR THINKING	POSITIVE			
SLEEPINESS	NEGATIVE			
UNHAPPINESS	NEGATIVE			
DIZZINESS	NEGATIVE			
MULTIPLE AFFECT ADJECTIVE CHECK LIST		P	132	225
HOSTILITY	NEGATIVE			
DEPRESSION	NEGATIVE			
ANXIETY	NEGATIVE			
PROFILE OF MOOD STATES		P	65	235
ANGER	NEGATIVE			
CONFUSION	NEGATIVE			
DEPRESSION	NEGATIVE			
FATIGUE	NEGATIVE			
TENSION	NEGATIVE			
VIGOR	POSITIVE			
COGNITIVE PERFORMANCE TESTS				
ADDITION	POSITIVE	P	(3)	124
CODING	POSITIVE	P	(3)	195
MAP COMPASS APPLICATIONS	POSITIVE	P	(4)	203
NUMBER COMPARISON	POSITIVE	P	(3)	199
PATTERN RECOGNITION	POSITIVE	P	(3)	120
TOWER TASK (POSSIBLE & OPTIMAL)	POSITIVE	P	(6)	265
REACTION TIME AND VIGILANCE TESTS				
SIMPLE REACTION TIME (RT)	NEGATIVE	C	300	240
CHOICE RT (LATENCY & ERRORS)	NEGATIVE	C	500	110
DUAL TASK VIGILANCE (HITS)	POSITIVE	C	800	175

Fig. 1

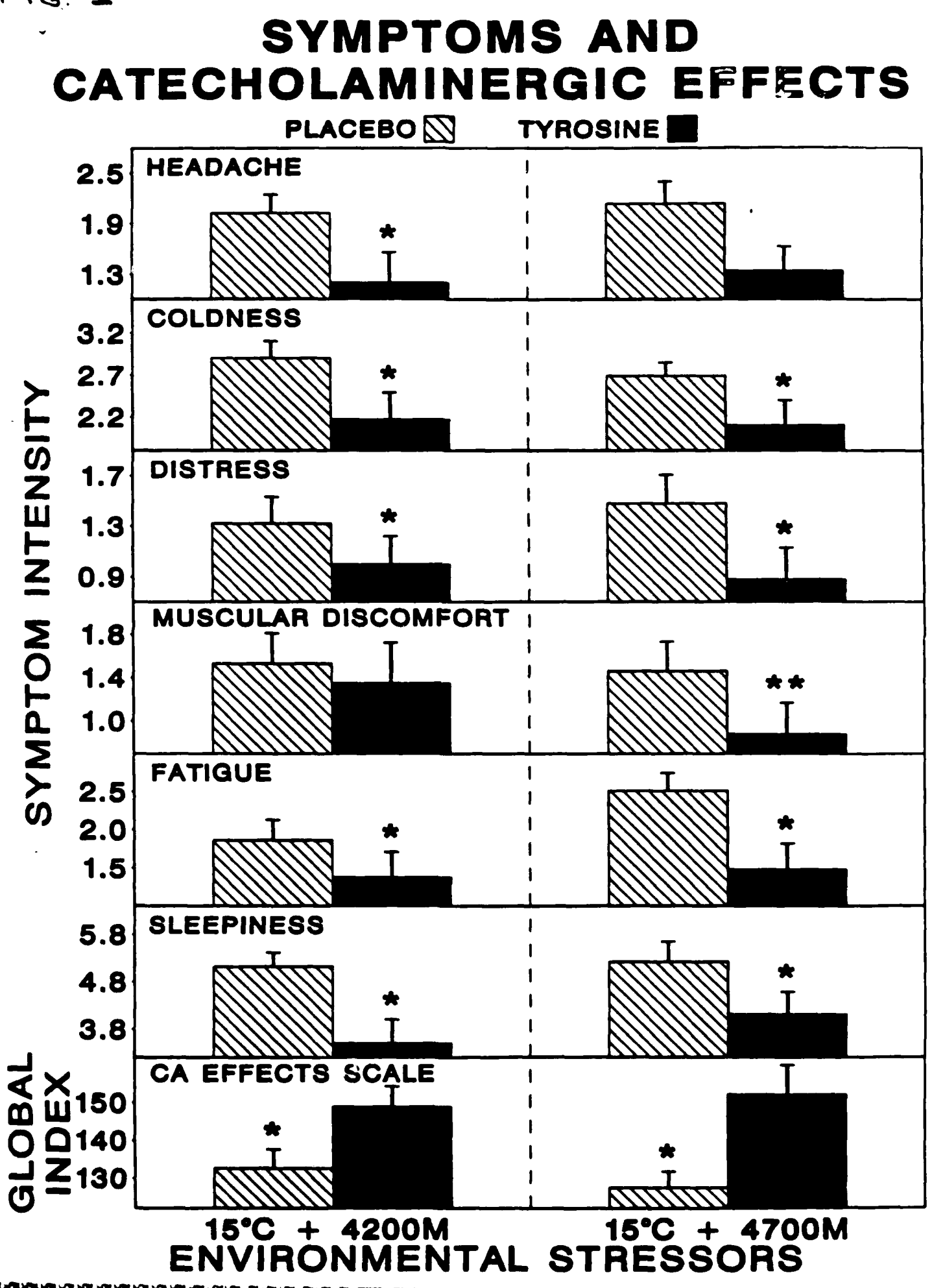

SYMPTOMS AND CATECHOLAMINERGIC EFFECTS
PLACEBO
TYROSINE
HEADACHE
2.5
1.9
1.3
COLDNESS
3.2
2.7
2.2
DISTRESS
1.7
1.3
0.9
MUSCULAR DISCOMFORT
1.8
1.4
1.0
FATIGUE
2.5
2.0
1.5
SLEEPINESS
5.8
4.8
3.8
CA EFFECTS SCALE
150
140
130
SYMPTOM INTENSITY
GLOBAL INDEX
15°C + 4200M
15°C + 4700M
ENVIRONMENTAL STRESSORS

FIG. 2

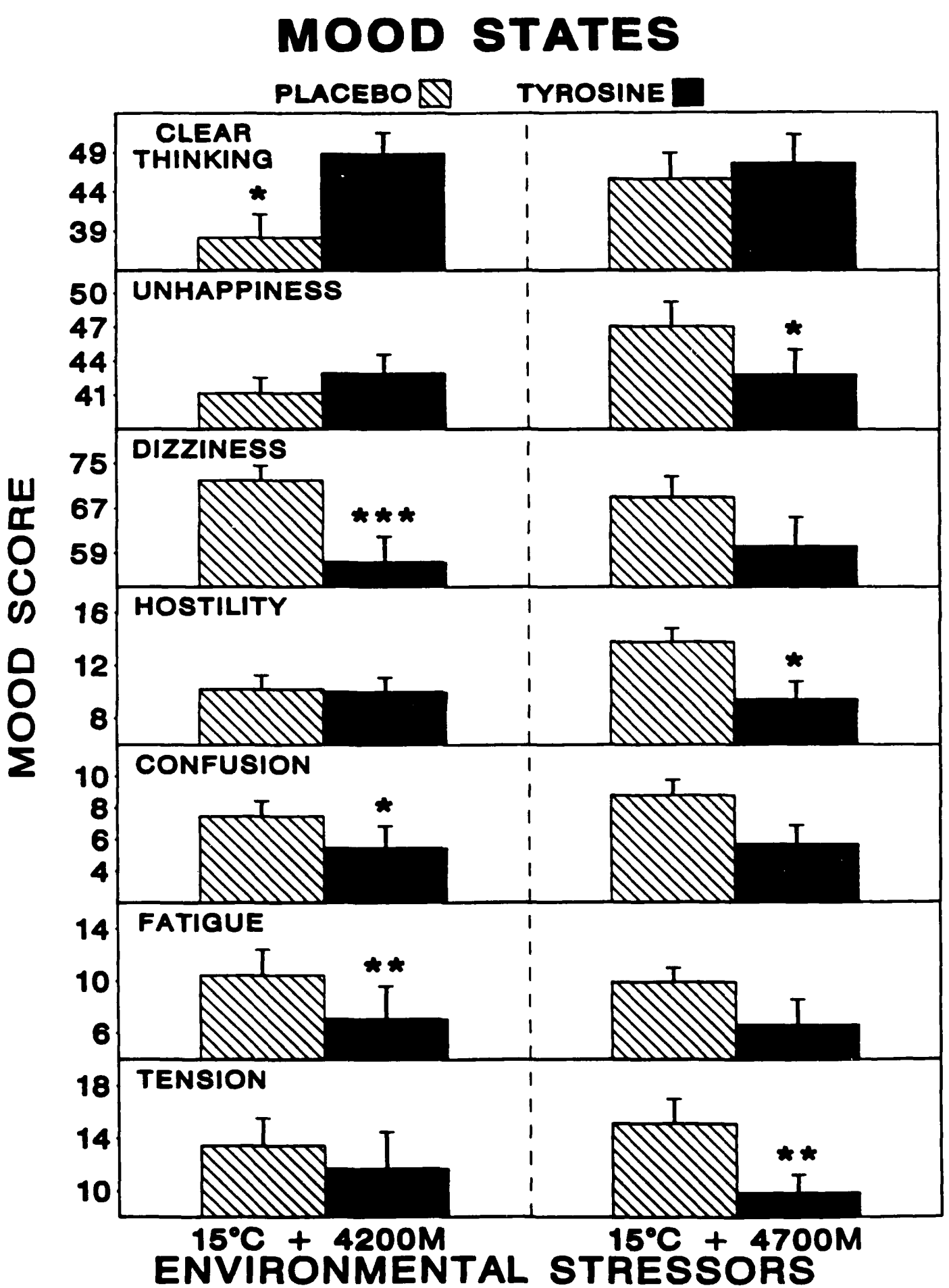
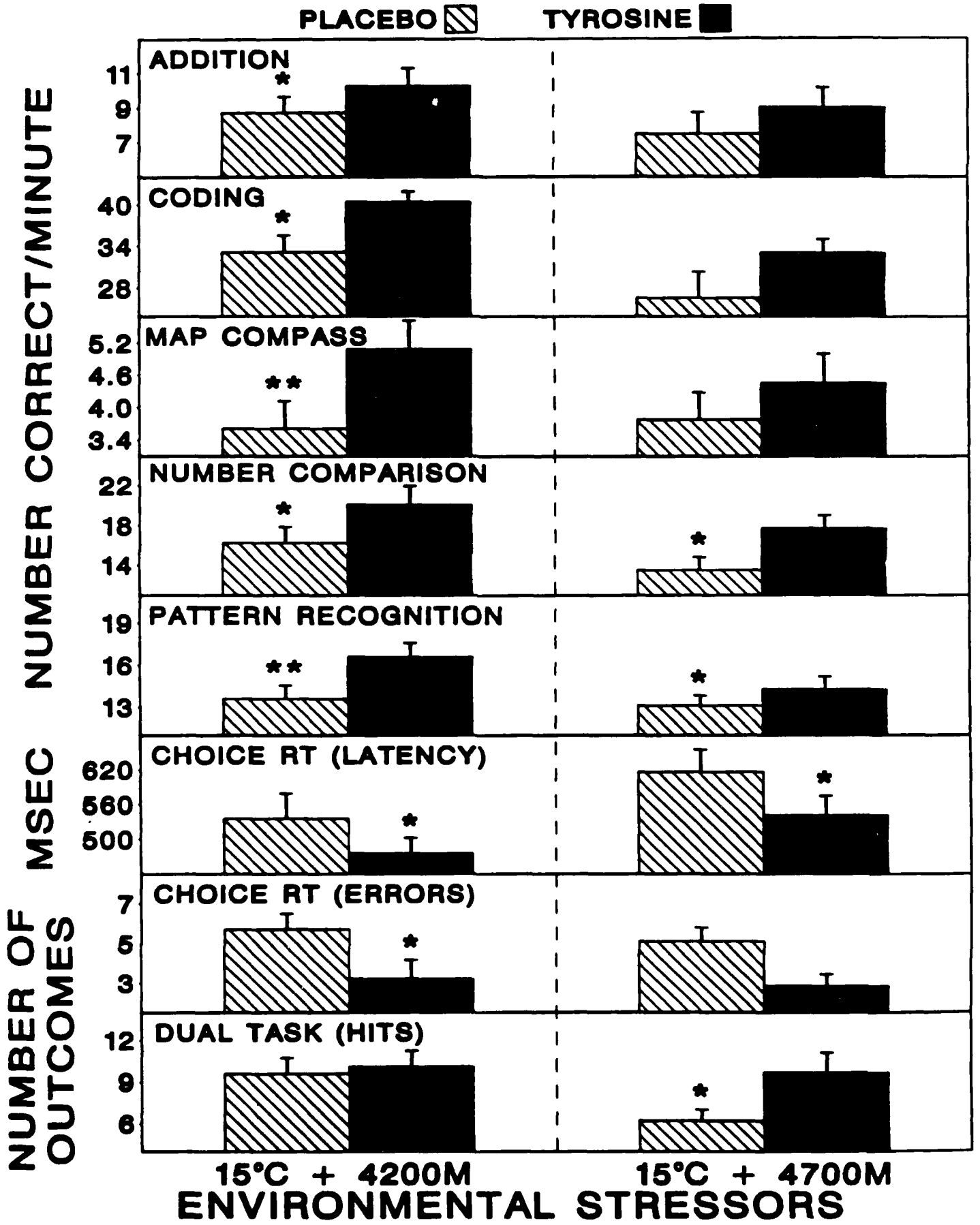

MOOD STATES
PLACEBO
TYROSINE
MOOD SCORE
CLEAR THINKING
49
44
39
*
UNHAPPINESS
50
47
44
41
*
DIZZINESS
75
67
59
***
HOSTILITY
16
12
8
*
CONFUSION
10
8
6
4
*
FATIGUE
14
10
6
**
TENSION
18
14
10
**
15°C + 4200M
15°C + 4700M
ENVIRONMENTAL STRESSORS

FIG. 3

COGNITIVE, REACTION TIME, AND VIGILANCE PERFORMANCE



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